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Note

Glycosylation of lactose. Synthesis of methyl *O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-β-D-galactopyranosyl-(1→4)-β-D-glucopyranoside and methyl *O*-β-D-galactopyranosyl-(1→4)-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-β-D-galactopyranosyl-(1→4)-β-D-glucopyranoside

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Numerous natural oligosaccharides, found either in the free state in human milk[1] or bound to a ceramide-like residue in blood-group-active glycosphingolipids of the red-cell membrane[2], contain a lactosyl residue, as the reducing end-group, substituted at O-3 of the D-galactopyranose unit by various sugars. The chemical synthesis of such structures may require a derivative of lactose having a free hydroxyl group at C-3 of the D-galactose unit, and permanent protective groups at all the other positions. Takamura *et al.*[3] have extensively used 1,6-anhydro-4′,6′-*O*-benzylidene-β-lactose as a starting material for their modifications of lactose; partial *O*-tosylation of this compound afforded them a way of functionalizing the 3′-position of lactose, albeit in 15% yield. Other investigators started with a 3′,4′-*O*-isopropylidene-lactose[4] or -lactoside[5,6], which was converted either into a 3′,4′-diol[4,5] or a fully esterified compound[6] apart from OH-3′. A D-galactopyranose unit having unsubstituted OH-3 and -4 is usually selectively glycosylated at O-3 but the regioselectivity of this reaction actually depends on the type of catalyst used[7], and, most probably, on the reactivity of the glycosylating agent[8]. Therefore, lactose derivatives having only one unprotected OH-3′, such as the one used by Ponpipom *et al.*[6] may be of a more reliable use for glycosylation.

Recently, we reported a one-step functionalization of methyl β-lactoside through its dibutylstannylene complex, affording good yields of methyl 3′-*O*-allyl-β-lactoside (**1**) with an excellent regioselectivity[9]. This convenient reaction will simplify the synthesis of the above-mentioned compounds, and also allow further modification at O-6′ for the preparation of branched structures. In order to

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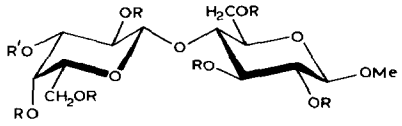
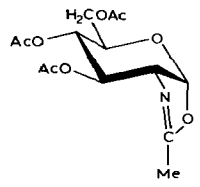
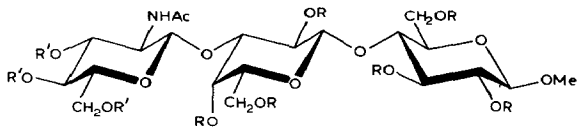
demonstrate such a possibility, we report herein the synthesis of a trisaccharide, methyl *O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-β-D-galactopyranosyl-(1→4)-β-D-glucopyranoside (**6**), and of a tetrasaccharide, methyl *O*-β-D-galactopyranosyl-(1→4)-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→3)-*O*-β-D-galactopyranosyl-(1→4)-β-D-glucopyranoside (**10**), which will be used for immunochemical and enzymic studies of the Ii blood-group system.

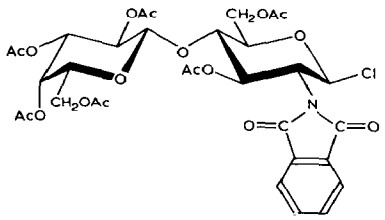




1 R = H, R′ = Allyl
2 R = *p*-BrC$_6$H$_4$CH$_2$, R′ = Allyl
3 R = *p*-BrC$_6$H$_4$CH$_2$, R′ = H

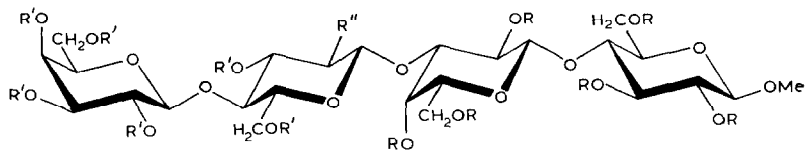
4





5 R = *p*-BrC$_6$H$_4$CH$_2$, R′ = Ac
6 R = R′ = H

7



8 R = *p*-BrC$_6$H$_4$CH$_2$, R′ = Ac, R″ = NPhthaloyl
9 R = R′ = Ac, R″ = NHAc
10 R = R′ = H, R″ = NHAc

Methyl 4-*O*-(3-*O*-allyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**1**) was prepared as previously described[9] and isolated, in crystalline form, from a mixture containing small proportions of unreacted methyl β-lactoside and isomeric or disubstituted compounds. Benzylation of the remaining groups of **1** failed to give a crystalline derivative, but the reaction of **1** with sodium hydride and *p*-bromobenzyl bromide[10] in *N*,*N*-dimethylformamide gave a pure, crystalline compound **2** in 65% yield. Removal of the *O*-allyl group with chlorotris(triphenylphosphine)rhodium afforded the crystalline alcohol **3** which, thus, was obtained in only three steps from methyl β-lactoside.

Condensation of **3** with 2-methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline[11] (**4**) in 1,2-dichloroethane in the presence of *p*-toluenesulfonic acid at 70° took place very sluggishly and required a five-molar excess of oxazoline, added at various times; the yield of the isolated crystalline trisaccharide **5** was only 42%. It is noteworthy that Takamura *et al.*[3] were able to glycosylate OH-3′ of 1,6-anhydro derivatives of lactose in much higher yields, under experimental conditions similar to ours; it is possible that in such compounds the $^1C_4$(D) conformation of the D-glucopyranose ring has a smaller hindering effect upon the condensation site. Compound **5** was conventionally *O*-deacetylated, and then hydrogenolyzed in 1,4-dioxane–methanol in the presence of palladium-on-charcoal and molecular sieves. The rate of hydrogenation was rather fast (15–30 min), although a small proportion of partially *O*-benzylated material remained present and required a more prolonged treatment. In the absence of molecular sieves, the reaction mixture became very acidic by formation of hydrogen bromide. When performed in the presence of the required amount of potassium hydroxide to neutralize the hydrogen bromide formed[12], the reaction stopped after cleavage of all the carbon–bromine bonds and thus an *O*-benzylated derivative could be obtained.

The free trisaccharide **6** was obtained in crystalline form after purification by column chromatography on silica gel. Its ^{1}H-n.m.r. spectrum showed a distinct signal at δ 4.66 for the anomeric proton of the 2-acetamido-2-deoxy-β-D-glucopyranosyl residue (H-1″, d, *J* 8.0 Hz), two close signals at δ 4.39 and 4.42 for the two other anomeric protons (H-1 and -1′, 2 d, *J* 7.0 Hz), and a signal at a field (δ 4.14) lower than those of other signals and which could be attributed to equatorial H-4′ of the D-galactopyranosyl residue.

Recently, Piller and Cartron[13] reported the presence in human serum of a β-(1→3)-*N*-acetyl-D-glucosaminyltransferase that transfers 2-acetamido-2-deoxy-D-glucose residues from UDP-2-acetamido-2-deoxy-D-glucose to terminal β-D-galactosyl groups linked (1→4) to D-glucose or 2-acetamido-2-deoxy-D-glucose residues in oligosaccharides, glycoproteins, glycolipids, and proteoglycans. When methyl β-lactoside was used as an acceptor, the product of the transferase reaction was found to be identical to the present synthetic trisaccharide **6**. In turn, synthetic **6** was a good acceptor for a β-(1→4)-D-galactosyltransferase from bovine milk[14] to give the lacto-*N*-*neo*tetraose sequence, β-D-Gal*p*-(1→4)-β-D-Glc*p*NAc-(1→3)-β-D-Gal*p*-(1→4)-β-D-GlcOCH$_3$ (**10**). Those two enzymic glycosylations are most probably involved in the biosynthesis of i blood-group active structures containing repeating units of *N*-acetyllactosamine.

The sequence of lacto-*N*-*neo*tetraose could be obtained from the derivative **3** of lactose by condensation with an oxazoline or a chloride derived from lactosamine. The reaction of the *O*-acetylated oxazoline derivative of *N*-acetyllactosamine[15] with alcohol **3** was found to proceed very sluggishly and gave only a 9% yield of the protected tetrasaccharide. A much better result was obtained when the phthalimido chloride[6,16,17] (**7**) was used in the presence of silver

trifluoromethanesulfonate and 2,4,6-trimethylpyridine[18]; after 3 days, the crystalline condensation product **8** was isolated in 68% yield after column chromatography on silica gel. The *p*-bromobenzyl groups were hydrogenolyzed as described for compound **5**, a much more prolonged treatment being however required. Hydrazinolysis removed *N*-phthaloyl and *O*-acetyl groups, and conventional acetylation in pyridine–acetic anhydride gave the *N,O*-acetylated tetrasaccharide **9** which was purified by column chromatography. Its ^{1}H-n.m.r. spectrum showed four distinct signals that could be attributed to each of the anomeric protons by use of decoupling techniques, and a widely separated pair of two doublets of doublets (δ 3.97 and 4.80) tentatively assigned to H-6 of the 2-acetamido-2-deoxy-D-glucose unit, the terminal D-glucose residue giving H-6 signals at δ 4.47 and ~4.1.

O-Deacetylation of **9** gave pure tetrasaccharide **10** which crystallized from methanol as a tetrahydrate. As with compound **6**, its ^{1}H-n.m.r. spectrum showed a distinct doublet at δ 4.68 for the anomeric proton of the 2-acetamido-2-deoxy-β-D-glucopyranosyl residue, three doublets at δ 4.38, 4.41, and 4.45 for the three other anomeric protons, and a characteristic signal at δ 4.13 for the equatorial H-4 of the internal D-galactopyranose residue.

Biological experiments performed with oligosaccharides **6** and **10** will be reported elsewhere.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Optical rotations were measured, at 20°, with a Roussel–Jouan electronic, digital micropolarimeter. All reactions were monitored by t.l.c. on plates of silica gel (with fluorescence indicator; layer thickness 0.25 mm; E. Merck, 60 F_{254}), and the products were detected by spraying the plates with 1:19 (v/v) conc. H_2SO_4–ethanol and heating on a hot plate. Silica gel Merck 60 (70–230 mesh) was used for column chromatography. ^{1}H-N.m.r. spectra were recorded at 250 MHz with a Cameca model STN 250 spectrometer, or at 400 MHz with a spectrometer constructed in this University for solutions in $CDCl_3$ and with tetramethylsilane as internal standard, or in D_2O with tetramethylsilane (0.2% solution in $CDCl_3$) as external reference. Microanalyses were performed by the Laboratoire Central de Micro-Analyse du C.N.R.S.

Methyl 4-O-[3-O-allyl-2,4,6-tri-O-(p-bromobenzyl)-β-D-galactopyranosyl]-2,3,6-tri-O-(p-bromobenzyl)-β-D-glucopyranoside (**2**). — A mixture of methyl 4-*O*-(3-*O*-allyl-β-D-galactopyranosyl)-β-D-glucopyranoside[9] (**1**; 3.96 g, 10 mmol), *p*-bromobenzyl bromide (30.0 g, 120 mmol), and NaH (2.88 g, 120 mmol) in *N,N*-dimethylformamide (120 mL) was stirred for 24 h at room temperature. The excess of hydride was decomposed by the addition of methanol to the cooled mixture. The solution was diluted with ether, washed with water, dried ($CaCl_2$), and evaporated. The residue crystallized from ether–hexane to give 9.17 g (65%) of **2**, m.p. 118–120°, $[\alpha]_D^{20}$ −3° (*c* 0.99, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 3.54 (s, 3 H, OMe), 4.27

and 4.34 (d each, 2 H, *J* 7.8 Hz, H-1,1′), 5.17–5.33 (m, 2 H, -CH=CH_2), 5.88–5.97 (m, 1 H, -C*H*=CH_2), and 7.08–7.46 (m, 24 H, arom.).

Anal. Calc. for $C_{58}H_{58}Br_6O_{11}$: C, 49.38; H, 4.14; Br, 34.00; O, 12.48. Found: C, 49.62; H, 4.27; Br, 34.21; O, 12.31.

*Methyl 2,3,6-tri-*O*-(*p*-bromobenzyl)-4-*O*-[2,4,6-tri-*O*-(*p*-bromobenzyl)-β-*D*-galactopyranosyl]-β-*D*-glucopyranoside* (**3**). — A solution of **2** (7.05 g, 5 mmol) in 9:4:1 (v/v) ethanol–1,2-dichloroethane–water (112 mL) was boiled under reflux for 24 h with chlorotris(triphenylphosphine)rhodium (325 mg, 0.35 mmol). The solvent was evaporated under vacuum. The product was purified by column chromatography on silica gel with 17:3 (v/v) toluene–ethyl acetate and crystallized from ethanol–hexane to give 3.81 g (56%) of **3**, m.p. 91–94°, $[\alpha]_D^{20}$ 0° (*c* 1.04, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 3.53 (s, 3 H, OMe), 4.27 and 4.35 (d each, 2 H, *J* 7.8 Hz, H-1,1′), and 7.08–7.48 (m, 24 H, arom.).

Anal. Calc. for $C_{55}H_{54}Br_6O_{11}$: C, 48.19; H, 3.97; Br, 35.00; O, 12.84. Found: C, 48.62; H, 4.12; Br, 34.65; O, 12.66.

*Methyl O-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl)-(1→3)-*O*-[2,4,6-tri-*O*-(*p*-bromobenzyl)-β-*D*-galactopyranosyl]-(1→4)-2,3,6-tri-*O*-(*p*-bromobenzyl)-β-*D*-glucopyranoside* (**5**). — A mixture of **3** (1.37 g, 1 mmol), oxazoline[11] **4** (0.59 g, 1.8 mmol), and *p*-toluenesulfonic acid (50 mg) in 1,2-dichloroethane (90 mL) was stirred under nitrogen for 26 h at 70°, additional amounts of **4** (0.49 g, 1.5 mmol, each time) being added after 12 and 20 h. T.l.c. (7:7:2, v/v, toluene–ether–methanol) showed one major spot (R_F 0.55) together with unreacted **3** (R_F 0.89) and **4** (R_F 0.38). The solution was cooled, diluted with dichloromethane, washed with water, and evaporated. The residue was chromatographed on silica gel with 19:1 (v/v) dichloromethane–acetone to give 0.71 g (42%) of **5**, m.p. 151–154°, $[\alpha]_D^{20}$ −20° (*c* 1.00, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.52, 1.97, 2.00 and 2.05 (4 s, 4 × 3 H, 4 Ac), 3.51 (s, 3 H, OMe), and 7.07–7.52 (m, 24 H, arom.).

Anal. Calc. for $C_{69}H_{73}Br_6NO_{19}$: C, 48.75; H, 4.33; Br, 28.21; N, 0.82; O, 17.89. Found: C, 48.98; H, 4.50; Br, 28.19; N, 1.03; O, 17.74.

*Methyl O-(2-acetamido-2-deoxy-β-*D*-glucopyranosyl)-(1→3)-*O*-β-*D*-galactopyranosyl-(1→4)-β-*D*-glucopyranoside* (**6**). — Compound **5** (0.575 g) was dissolved in methanol (30 mL) and treated overnight at room temperature with M sodium methoxide in methanol (1.6 mL). The mixture was made neutral with Amberlite IR 120 (H^+) ion-exchange resin and filtered, and the filtrate evaporated. The residue was dissolved in 4:1 (v/v) methanol–1,4-dioxane (20 mL) and hydrogenated at room temperature and atmospheric pressure in the presence of 5% Pd–C (100 mg) and powdered 4A molecular sieves (1 g). After 30 min, t.l.c. (3:2:1, v/v, ethyl acetate–2-propanol–water) showed no more starting material (R_F 0.80), a major compound (R_F 0.10), and a small proportion of a partially *O*-benzylated product (R_F 0.60). The mixture was filtered, and the filtrate further hydrogenated for 90 min in the presence of fresh amounts of 5% Pd–C (100 mg). After filtration and evaporation, the residue was chromatographed on silica gel with 3:2:1 (v/v) ethyl

acetate–2-propanol–water to give 0.128 g (68%) of **6**, which crystallized from methanol, m.p. 244° (dec.), $[\alpha]_D^{20}$ +6° (*c* 0.95, water); ^{1}H-n.m.r. (D_2O): δ 2.02 (s, 3 H, $COCH_3$), 3.54 (s, 3 H, OCH_3), 4.14 (d, 1 H, H-4′), 4.39 and 4.42 (d each, 2 H, *J* 7.0 Hz, H-1,1′), and 4.66 (d, 1 H, *J* 8.0 Hz, H-1″).

Anal. Calc. for $C_{21}H_{37}NO_{16}$: C, 45.08; H, 6.67; O, 45.75. Found: C, 44.99; H, 6.66; O, 45.57.

Methyl O-*(2,3,4,6-tetra*-O-*acetyl-β*-D-*galactopyranosyl)-(1→4)*-O-*(3,6-di*-O-*acetyl-2-deoxy-2-phthalimido-β*-D-*glucopyranosyl)-(1→3)*-O-[*2,4,6-tri*-O-*(p-bromobenzyl)-β*-D-*galactopyranosyl]-(1→4)-2,3,6-tri*-O-*(p-bromobenzyl)-β*-D-*glucopyranoside* (**8**). — A solution of **3** (1.37 g, 1 mmol) in dichloromethane (40 mL) was stirred for 1 h under nitrogen in the presence of 2,4,6-trimethylpyridine (0.184 g, 1.52 mmol) and powdered 4A molecular sieves (5 g). Silver trifluoromethanesulfonate (0.333 g, 1.30 mmol) was added; the mixture was cooled to 0°, and a solution of 3,6-di-*O*-acetyl-2-deoxy-2-phthalimido-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosyl chloride[6,16,17] (**7**, 0.961 g, 1.30 mmol) in dichloromethane (40 mL) was added dropwise. The mixture was stirred for 72 h at room temperature, additional amounts of **7** (0.519 g, 0.70 mmol), silver trifluoromethanesulfonate (0.180 g, 0.70 mmol), and 2,4,6-trimethylpyridine (0.097 g, 0.80 mmol) being added after 24 h. After dilution with dichloromethane and filtration, the solution was successively washed with cold M HCl and water, and then evaporated. The residue was chromatographed on silica gel with 17:3 (v/v) toluene–ethyl acetate to give 1.42 g (68%) of **8**, which crystallized from ethanol, m.p. 99–102°, $[\alpha]_D^{20}$ −37° (*c* 0.98, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.87, 1.96, 1.97, 2.02, 2.09, 2.14 (s, 18 H, 6 OAc), 3.46 (s, 3 H, OMe), 4.57 (d, 1 H, $J_{1,2}$ 8 Hz, H-1‴), 4.99 (dd, 1 H, $J_{2,3}$ 10.5, $J_{3,4}$ 3.5 Hz, H-3‴), 5.16 (dd, 1 H, H-2‴), 5.36 (dd, 1 H, $J_{4,5}$ 1.0 Hz, H-4‴), 5.60 (d, 1 H, $J_{1,2}$ 8.5 Hz, H-1″), 5.79 (dd, 1 H, $J_{2,3}$ 10.5, $J_{3,4}$ 8.0 Hz, H-3″), and 6.76–7.65 (m, 28 H, arom.).

Anal. Calc. for $C_{87}H_{89}Br_6NO_{28}$: C, 50.33; H, 4.32; Br, 23.10; N, 0.67; O, 21.58. Found: C, 50.05; H, 4.36; Br, 23.36; N, 0.75; O, 21.56.

Methyl O-*β*-D-*galactopyranosyl-(1→4)*-O-*(2-acetamido-2-deoxy-β*-D-*glucopyranosyl)-(1→3)*-O-*β*-D-*galactopyranosyl-(1→4)-β*-D-*glucopyranoside* (**10**). — Compound **8** (1.0 g) was dissolved in 3:2 (v/v) methanol–1,4-dioxane (60 mL) and hydrogenated at room temperature and atmospheric pressure in the presence of 5% Pd–C (200 mg) and powdered 4A molecular sieves (2 g). After 30 min, t.l.c. (3:2:1, v/v, ethyl acetate–2-propanol–water) showed the presence of some partially *O*-benzylated products. The mixture was filtered, and the filtrate hydrogenated for 5 days in the presence of fresh catalyst (200 mg). After filtration and evaporation, the residue was dissolved in ethanol (30 mL) and treated for 2 h under reflux with 85% hydrazine hydrate (10 mL). T.l.c. (1:3:2, v/v, dichloromethane–methanol–conc. NH_3) showed a major product (R_F 0.30). The mixture was cooled and evaporated, and the residue acetylated for 24 h at room temperature in 4:1 (v/v) pyridine–acetic anhydride. After conventional processing, the crude product was purified by column chromatography on silica gel with 17:3 (v/v) toluene–ethyl

acetate to afford **9** (0.35 g, 59%); ^{1}H-n.m.r. ($CDCl_3$): δ 1.89–2.15 (39 H, 13 Ac), 3.48 (s, 3 H, OMe), 3.97 (dd, 1 H, $J_{6a,6b}$ 12, $J_{5,6a}$ 3 Hz, H-6″a), 4.35 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1′), 4.39 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.47 (dd, 1 H, $J_{6a,6b}$ 12 Hz, $J_{5,6b}$ 2 Hz, H-6b), 4.55 (d, 1 H, $J_{1,2}$ 8 Hz, H-1‴), 4.69 (d, 1 H, $J_{1,2}$ 8 Hz, H-1″), 4.80 (dd, 1 H, $J_{5,6b}$ 2 Hz, H-6″b), 4.90 (dd, 1 H, $J_{2,3}$ 10 Hz, H-2), 4.97–5.02 (m, 2 H, H-2′,3‴), 5.11–5.24 (m, 3 H, H-3,3″,2‴), 5.32 (d, 1 H, $J_{3,4}$ 3 Hz, H-4′), 5.34 (d, 1 H, $J_{2,NH}$ 9.6 Hz, NH), and 5.37 (d, 1 H, $J_{3,4}$ 3 Hz, H-4‴).

Compound **9** (0.35 g) was dissolved in methanol (20 mL) and treated with M sodium methoxide in methanol (1 mL). After 15 h at room temperature, the solution was made neutral with Amberlite IR 120 (H^+) ion-exchange resin, filtered, and evaporated. Crystallization from methanol afforded 0.165 g (80%) of **10**, m.p. 205° (dec.), $[\alpha]_D^{20}$ +4° (*c* 0.99, water); ^{1}H-n.m.r. (D_2O): δ 1.99 (s, 3 H, NAc), 3.54 (s, 3 H, OCH_3), 4.13 (d, 1 H, H-4′*e*), 4.38, 4.41, and 4.45 (d each, 3 H, *J* 7.5 Hz, H-1,1′,1‴), and 4.68 (d, 1 H, *J* 8.5 Hz, H-1″).

Anal. Calc. for $C_{27}H_{47}NO_{21} \cdot 4\ H_2O$: C, 40.85; H, 6.98; N, 1.76; O, 50.40. Found: C, 41.01; H, 6.81; N, 1.81; O, 50.37.

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